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# A Mathematical Model For Interaction Macrophages, T Lymphocytes and Cytokines at Infection of Mycobacterium tuberculosis with Age Influence

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***Abstract.*** Tuberculosis (TB) is still a health problem in the world, because of the increasing prevalence and treatment outcomes are less satisfactory. This is presumably due to a complete lack of understanding of the role of the immune system to infection Mycobacterium tuberculosis (Mtb). Currently it is known that the immune response plays a role in controlling the development of the germ cells are macrophages, T lymphocytes and cytokines. This study has made a mathematical model of the interaction between macrophages, T lymphocytes and cytokines with Mtb infection in the lungs. Effect of age was observed through disparate data, young (3 months) and old (18 months). Runge Kutta method order-4 is used to solve the system of non-linear differential equations of the first order. Growth of bacteria (extracellular and intracellular) tends to increase up to 3 months, either in old mice and young mice. Behavior of T cells dropped drastically. Concentration of IL-2 and IL-4 is likely to increase at the beginning of infection, TNF-$\alpha$ , IL-10, IFN-$\gamma$ and IL-12 increased. Resting macrophages tend to fall, infected macrophages tended to rise and activated macrophages fluctuate in the first 3 months.

Key-Words: *mathematical models, Mycobacterium tuberculosis, macrophages, T lymphocytes, cytokines*.

## 1. Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (Mtb) and infected almost a third of the world population. An approximated 8.9 million people with TB with 3 million people die per year. Indonesia is the third country in the world in order of the number of TB patients after India (30%) and China (15%) with a percentage of 10% of the total TB patients in the world.

A cell-mediated immune response is essential for control of Mtb in the lungs particularly macrophages and T lymphocytes. Alveolar macrophages that serve as a haven for bacteria as well as to eliminate the bacteria. Eliminates bacteria depends on cytokines IFN-$\gamma$ , TNF-$\alpha$ , IL-2, IL-10 secretion by T cell. T lymphocytes have two important roles in TB infection. First, produce a variety of cytokines in the development of cell-mediated immune response. Second, eliminate infected macrophages through the process of apoptosis. There are four mechanisms of CD8+ T cells contribute to the control of Mtb: (1) the release of cytokines, (2) cytotoxicity via the granule-dependent exocytosis, (3) mediated cytotoxicity in Fas / Fas ligand interaction, and (4) Directly active as microbicidal. Activity cytotoxic of CD8+ T cells in the process of apoptosis through Fas - Fas ligand pathway and killing through perforin and granulysin. In humans, CD8+ T cells can kill bacteria through the release of intracellular antimicrobial peptide granulysin [3]. CD4+ T cell contributes to TB infection activates macrophages through the production of various cytokines, such as IL-10 and IFN-$\gamma$ for the lysis of infected macrophages. Increased activation of macrophages in fagositosis can eliminate extracellular bacteria, while lysis process serves chronically infected macrophages to release Mtb [2] .

Interleukin-10 (IL-10) is a cytokine that is immunoregulator. These cytokines play an important role in down-regulation, including inhibition of macrophage activation. Besides, IFN-$\gamma$ is a cytokine that is essential in activating macrophages to eliminate Mtb and involved in the process of Tho into Th1 differentiation. Another important cytokine is IL-4 and IL-12. IL-12 is a key cytokine for Th1 type. This cytokine is produced by activating macrophages and infected macrophages in-clicking antigen stimulation. IL-12 as well as the regulator primarily to induce differentiation into Th1 lymphocytes, suppress the production of IFN-$\gamma$ . Cytokine IL-4 is a Th2 cell prototype. These cytokines are also involved in the process of Tho into Th1 differentiation. The role of IL-4 in tuberculosis infection is still controversial.

Mathematical models of Mtb infection in humans and mice were developed by Wigginton [4]. The model that has been developed is not directly involve cytokines IL-2 and TNF-as well as CD8 + T lymphocytes. Whereas

cytokines TNF-$\alpha$ and CD8 + T lyarehocytes in TB infection is very important. On TB infection, cytokines TNF-$\alpha$ synergize with IFN-$\gamma$ in activating macrophages in producing various kinds of substances that can suppress the growth of Mtb.

Mathematical models of Mtb infection in humans and mice were developed by Friedman [7] with the involvement of the influence of age. The model does not directly involve the cytokines IL-4, TNF-$\alpha$, and resting macrophages. Whereas IL-4 inhibits activated macrophages, while macrophages and resting circulating equilibrium disrupted by activated macrophages and infected macrophages such resting macrophages depend on time.

This study makes a mathematical model interactions, immune system and Mtb involving populations of CD4+, CD8+ T cell; cytokines include interleukin-12 (IL-12), IL-4, IL-10, IL-2, TNF-$\alpha$ and IFN-$\gamma$; infected macrophages, resting macrophages and activated macrophages, the bacteria comprising the extracellular bacteria and intracellular bacteria involving the influence of age.

## 2. Material and Methods

### 2.1 Material

### 2.1.1 The Mathematical Model

Mathematical model of the interaction of macrophages and T lymphocytes forms a system of nonlinear differential equations of the first order. The model consists of 13 equations: three equations macrophages, six equations cytokines, two equations T lymphocytes, two equations bacteria. Explanations and models are given below.

### 2.1.2 The model equations

**Macrophage dynamics**. The equation that describes the rate of change of macrophage populations during Mtb infection is given in (1) - (3).

$$\frac{dM_R(t)}{dt} = sr_M + \alpha_{4A}(M_A(t) + w_2 M_I(t)) + sr_{4B}\left(\frac{F_\alpha(t)}{F_\alpha(t) + f_8 I_{10}(t) + s_{4b}}\right) - k_2 M_R(t)\left(\frac{B_E(t)}{B_E(t) + c_9}\right) - k_3 M_R(t)\left(\frac{I_\gamma(t)}{I_\gamma(t) + f_1 I_4(t) + s_1}\right)\left(\frac{B_T(t) + \beta F_\alpha(t)}{B_T(t) + \beta F_\alpha(t) + c_8}\right) - \mu_{MR}.M_R(t) \quad \text{.....(1)}$$

$$\frac{dM_A(t)}{dt} = k_3 M_R(t)\left(\frac{I_\gamma(t)}{I_\gamma(t) + f_1 I_4(t) + s_1}\right)\left(\frac{B_T(t) + \beta F_\alpha(t)}{B_T(t) + \beta F_\alpha(t) + c_8}\right) - k_4 M_A(t)\left(\frac{I_{10}(t)}{I_{10}(t) + c_3 I_\gamma(t) + c_4}\right) + k_{3A} M_I(t)\left(\frac{I_\gamma(t)}{I_\gamma(t) + a_2}\right) - \mu_{MA}.M_A(t) \quad \text{....(2)}$$

$$\frac{dM_I(t)}{dt} = k_2 M_R(t)\left(\frac{B_E(t)}{B_E(t) + c_9}\right) - k_{17}.M_I(t)\left(\frac{B_I(t)^2}{B_I(t)^2 + (N.M_I(t))^2}\right) - k_{14b} M_I(t)\left(\frac{F_\alpha(t)}{F_\alpha(t) + f_9 I_{10}(t) + s_{4b}}\right) + k_4 M_A(t)\left(\frac{I_{10}(t)}{I_{10}(t) + c_3 I_\gamma(t) + c_4}\right) - k_{3A} M_I(t)\left(\frac{I_\gamma(t)}{I_\gamma(t) + a_2}\right) - k_{14a} N.N_{fracc}\left(\frac{M_I(t)(T_8(t) + w_3 T_4(t))}{c_4.M_I(t) + (T_8(t) + w_3 T_4(t))}\right) - \mu_{MI} M_I(t) \quad \text{...(3)}$$

**Explanation:**

Changes in resting macrophages (1) influenced by the production of alveolar macrophages ( $sr_M$ ), move from activated macrophages $\alpha_{4A}$ and infected macrophages $w_2.\alpha_{4A}(0 < w_2 < 1)$, with the help of TNF-$\alpha$ on the recruitment rate $sr_{4B}$, the changes become infected macrophages $k_2$, activated macrophages $k_3$ as well as changes to the natural mortality rate $\mu_{MR}$ respectively. Changes activated macrophages (2) is affected by a change in resting macrophages become activated $k_3$, activated macrophages undergo deactivation $k_4$, changes become infected macrophages become activated $k_{3A}$, and the rate of natural mortality $\mu_{MA}$. Changes in infected macrophages (3) consecutive influenced by changes in resting macrophages become infected macrophages $k_2$, infected macrophages undergo a process of release $k_{17}$, changes in infected macrophages become activated macrophages $k_4$, infected macrophages become activated macrophages $k_{3A}$, infected macrophages undergo apoptosis $k_{14a}$ as well as the rate of natural mortality $\mu_{MA}$.

**Cytokines dynamics**. Equation that describes the rate of change in cytokine concentrations given in (4) - (9).

$$\frac{dI_{10}(t)}{dt} = \delta_7 M_A(t)\left(\frac{s_6}{I_{10}(t) + f_6 I_\gamma(t) + s_6}\right) + k_{7av} M_I(t)\left(\frac{c_{7a}}{I_{10}(t) + c_{7a}}\right) + \alpha_{16} T_4(t) + \alpha_{18} T_8(t) - \mu_{I10}.I_{10}(t) \quad ...(4)$$

$$\frac{dF_\alpha(t)}{dt} = \alpha_{30} M_I(t) + \alpha_{31} M_A(t)\left(\frac{I_\gamma(t) + \beta_2 B_T(t)}{\beta_2 B_T(t) + I_\gamma(t) + f_1 I_4(t) + f_7 I_{10}(t) + s_{10}}\right) + \alpha_{32} T_4(t) + \alpha_{33} T_8(t) - \mu_{F_\alpha}.F_\alpha(t) \quad ...(5)$$

$$\frac{dI_\gamma(t)}{dt} = s_g\left(\frac{B_T(t)}{B_T(t) + c_{10}}\right)\left(\frac{I_{12}(t)}{I_{12}(t) + s_7}\right) + \left(\alpha_u T_4(t) + \alpha_y T_8(t)\right)\left(\frac{I_{12}(t) + M_A(t)}{I_{12}(t) + M_A(t) + f_4 I_{10}(t) + s_4}\right) + \alpha_{5C} M_I(t) - \mu_{I\gamma}.I_\gamma(t) \quad ...(6)$$

$$\frac{dI_{12}(t)}{dt} = \alpha_{23} M_R(t)\left(\frac{B_E(t)}{B_E(t) + c_{23}}\right) + \alpha_{81} M_A(t)\left(\frac{c_{81}}{c_{81} + I_{10}(t)}\right) - \mu_{I12} I_{12}(t) \quad ...(7)$$

$$\frac{dI_2(t)}{dt} = k_{10} T_4(t) - (k_{11} T_4(t) + k_{12} T_8(t))\left(\frac{I_2(t)}{I_2(t) + c_{100}}\right) - \mu_{I2} I_2(t) \quad ...(8)$$

$$\frac{dI_4(t)}{dt} = \alpha_{112} T_4(t) - \mu_{I4} I_4(t) \quad ...(9)$$

**Explanation:**

IL - 10 (4) is produced mainly by activating macrophages with the rate $\delta_7$, this process is inhibited by IFN-$\gamma$ and IL -10. IL - 10 is also produced by infected macrophages at a rate of $k_{7av}$, the rate of CD4 + lymphocytes $\alpha_{16}$ and CD8 + T cell $\alpha_{18}$ as well as on the rate of degradation at rate of $\mu_{I10}$. TNF-$\alpha$ ( 5 ) is produced by macrophages infected with the rate $\alpha_{30}$, TNF-$\alpha$ is produced by activated macrophages with rate $\alpha_{31}$ , this process is inhibited by IL - 4 and IL - 10 . TNF-$\alpha$ is also produced by CD4 + T cell at a rate of $\alpha_{32}$ and on the rate of CD8 + T cell $\alpha_{33}$ as well

as on the rate of degradation $\mu_{F_\alpha}$ . IFN-$\gamma$ (6) is produced by Natural Killer cells (NK) in the rate $s_g$ . IFN-$\gamma$ is also produced by CD4 + T cell and the rate of CD8 + T cell in the rate of IFN-$\gamma$ produced by infected macrophages at a rate of $\alpha_u$ and on the rate of degradation $\mu_{I\gamma}$ . IL-12 (7) is produced by resting macrophages in response infection at a rate of $\alpha_{23}$, also produced by activated macrophages at a rate of $\alpha_{81}$ and degradation at a rate of $\mu_{I12}$. IL - 2 ( 8 ) is produced by CD4 + T cells and the rate $k_{10}$ of consumption by CD4 + T cells and CD8 + at different speeds $k_{11}$ and $k_{12}$ as well as degradation rate $\mu_{I2}$. IL-4 (9) only produced by CD4 + T cells and degraded at a rate of $\mu_{I4}$.

**T cell dynamics**. For T cell dynamics given in Equation (10) – (11).

$$\frac{dT_8(t)}{dt} = \lambda_x(M_A(t) + w_2 M_I(t))I_{12}(t) + s_r\left(\frac{F_\alpha(t)}{F_\alpha(t) + f_8.I_{10}(t) + s_{4b}}\right) + k_{44}T_8(t)\left(\frac{I_2(t)}{I_2(t) + c_{100}}\right)$$
$$- \mu_{Tc\gamma}T_8(t)M_A(t)\left(\frac{I_\gamma(t)}{I_\gamma(t) + c}\right) - \mu_{T8}T_8(t) \quad ...(10)$$

.

$$\frac{dT_4(t)}{dt} = \lambda_z M_A(t)I_{12}(t) + sr_{3B2}\left(\frac{F_\alpha(t)}{F_\alpha(t) + f_8.I_{10}(t) + s_{4b}}\right) + k_{13}T_4(t)\left(\frac{I_2(t)}{I_2(t) + c_{110}}\right)$$
$$- \mu_{T\gamma}T_4(t)M_A(t)\left(\frac{I_\gamma(t)}{I_\gamma(t) + c}\right) - \mu_{T4}T_4(t) \quad ...(11)$$

**Explanation :**

CD8 + T cells (10) arrive at infection at a rate of $\lambda_x$ . Recruitment of CD8 + T cells at the rate $s_r$ proliferation of IL-2 on the rate $k_{44}$ , the induction of CD8 + T cell apoptosis in the rate $\mu_{Tc\gamma}$ , and the rate of natural mortality $\mu_{T8}$. CD4 + T cells (11) arrive infections at the rate $\lambda_z$ . Recruitment of CD8 + T cells at the rate $sr_{3B2}$ , proliferation of IL-2 on the rate $k_{13}$ , the induction of CD8 + T cell apoptosis in the rate $\mu_{T\gamma}$ , and the rate of natural mortality $\mu_{T4}$ .

**Bacterial dynamics.** For bacterial dynamics given in Equation (12) – (13).

$$\frac{dB_E(t)}{dt} = \alpha_{20}B_E(t) - k_5 M_A(t)B_E(t) - n_3.k_2 M_R(t)\left(\frac{B_E(t)}{B_E(t) + c_9}\right)$$
$$+ k_{14a}N.N_{fracc}\left(\frac{M_I(t)(T_8(t) + w_3T_4(t))}{c_4.M_I(t) + (T_8(t) + w_3T_4(t))}\right) + k_{17}N.M_I(t)\left(\frac{B_I^2(t)}{B_I^2(t) + \left(N.M_I(t)\right)^2}\right)$$
$$+ k_{14b}.N.M_I(t)\left(\frac{F_\alpha(t)}{F_\alpha(t) + f_8 I_{10}(t) + s_{4b}}\right) + \mu_I B_I(t) \quad ...(12)$$

.

$$\frac{dB_I(t)}{dt} = \alpha_{19} B_I(t)\left(1 - \frac{B_I^2(t)}{B_I^2(t) + \left(N.M_I(t)\right)^2}\right) + n_3.k_2 M_R(t)\left(\frac{B_E(t)}{B_E(t) + c_9}\right)$$
$$- k_{17} N.M_I(t)\left(\frac{B_I^2(t)}{B_I^2(t) + \left(N.M_I(t)\right)^2}\right) - k_{14a} N\left(\frac{M_I(t)(T_8(t) + w_3 T_4(t))}{c_4 + M_I(t) + (T_8(t) + w_3 T_4(t))}\right)$$
$$- k_{14b} N.M_I(t)\left(\frac{F_\alpha(t)}{F(t)_\alpha + f_8.I_{10}(t) + s_{4b}}\right) - \mu_I B_I(t) \qquad ...(13)$$

**Explanation:**

Extracellular bacteria growing at the rate $\alpha_{20}$. The bacteria are killed by activated macrophages at rate $k_5$ and resting macrophages at a rate $k_2$, infected macrophages undergo apoptosis $k_{14a}$, infected macrophages undergo apoptosis ( $k_{17}$), TNF-$\alpha$ induced apoptosis of infected macrophages with intracellular bacteria natural mortality rate $\mu_I$.

## 2.2 Methods

### 2.2.1 Computer simulations

Numerical simulations are used in a mathematical model to obtain the behavior of each variable is the Runge Kutta method of order 4 with Program Matlab version 7.0.

#### 2.2.2 Parameter values

All the variables and parameters used in equations (1) - (13) are given in the table. Table 1 contains the initial value derived from Friedman, 2008 and Sud, 2006. Table 2 contains the parameter differences between young mice and old mice. Table 3 contains all of the parameters used in equations (1)-(13). When no data is available, was estimated, average, Adjustment or proportional data. Numerical simulation started on day 7 after Mtb infection. The units used for the cell is the number of cells per milliliter of bronchoalveolar lavage (BAL), whereas the concentration of cytokines was picograms per milliliter of BAL.

The rate of growth and decay ( $\alpha_{19}, \alpha_{20}, \mu_{I4}, \mu_{I12}\ \mu_{I10}, \mu_g$ ) is given by using the following standard formula

$$\frac{dN(t)}{dt} = r.N(t) \quad \text{to get} \quad r = \frac{\ln 2}{Life\,time}$$

## 3. Results

Based on the mathematical model equations (1) - (13), used Runge Kutta order 4, Table 1,2 and 3 as well as using Matlab.7.0 software (see figure 1 and 2).

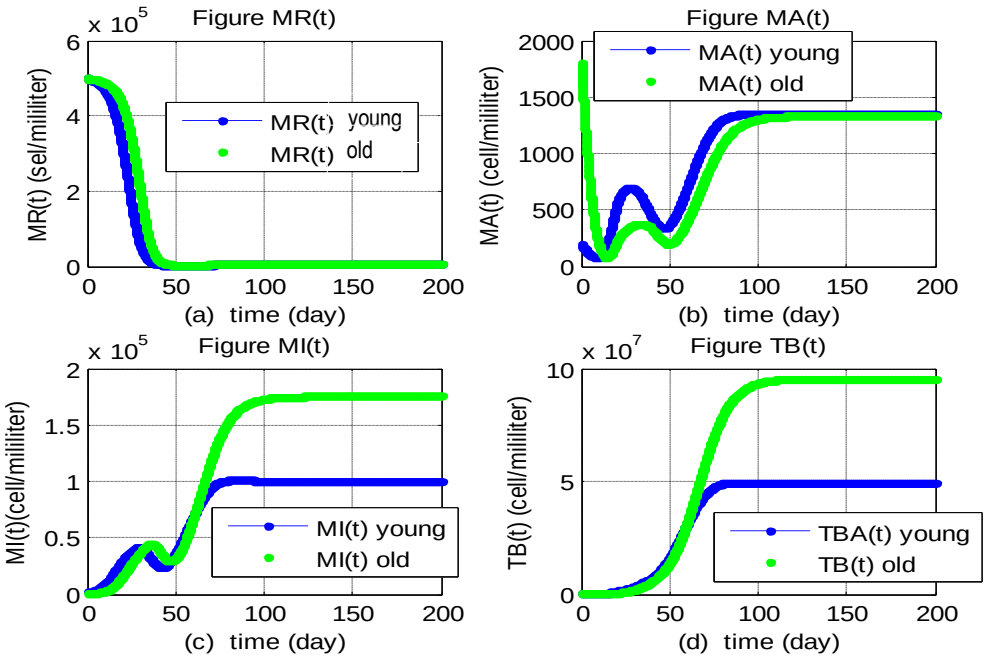


**Figure 1** Simulation result of total bacteria( TB), Resting macrophages (MR), infected macrophages (MI) and activated macrophages (MA) without TNF-$\alpha$

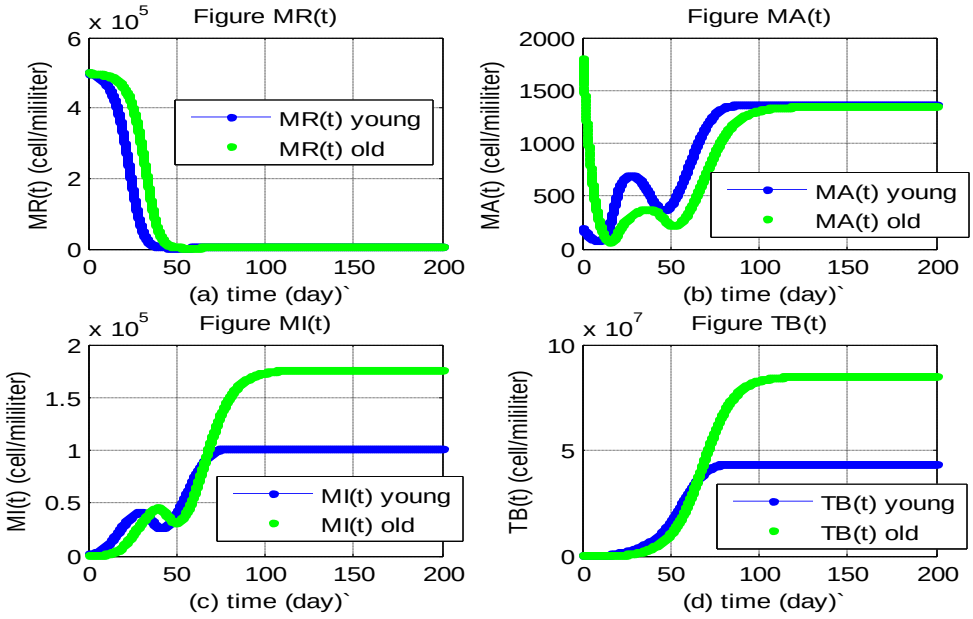


**Figure 2** Simulation result of total bacteria (TB), Resting macrophages (MR), infected macrophages (MI) and activated macrophages (MA) with TNF-$\alpha$ .

Figure 1 behavior of macrophages and total bacteria. Figure 1 and 2 consist of a). Resting macrophages for young and old mice. b). Activated macrophages for the young and old mice. c) Infected macrophages are higher in young mice in the first month. d) The behavior of higher total bacterial old mice after a month-3. Figure 2 is the behavior of macrophages and total bacteria involved. Bacterial growth is likely to increase up to 3 months, both young mice and old mice and old mice to bacterial counts higher than the number of bacteria in a mouse model. Total higher when bacteria when compared to without involving. Drawings for lymphocytes T CD4 + and CD8 + as well as cytokine not displayed.

## 4. Conclusion

1) Mathematical model of the interaction of macrophages with T cells in response to infection of Mtb in human form a system of ordinary differential equations, nonlinear involving 13 variables, namely macrophages (resting macrophages, activated macrophages and infected macrophages), T lymphocytes (CD4 + T cells and CD8 + T cells) and cytokines (IL-2, IL-4, IL-10, IL-12, IFN-$\gamma$, TNF-$\alpha$) and bacterial extracellular and intracellular bacteria.
2) Bacterial growth is likely to increase up to 3 months, both young mice and old mice and old mice to bacterial counts higher than the number of bacteria in young mice.
3) Decreased number of T cells ( CD4 + T cells and CD8 + T cells ) when the case without the case with TNF -$\alpha$ and TNF -$\alpha$ and IL - 4 mice both young and old rats . For the case without TNF -$\alpha$ and IL - 4, increa(g the number of T cells ( CD4 ) cells and CD8 + T cells ) mice both young and old mice.
4) Cytokine IL - 10, TNF -$\alpha$ and IFN-$\gamma$ ,e likely to increase, both young mice and old mice , while IL - 4 and IL - 2 tended to decrease.
5) Resting macrophages decreased dramatically, is caused by resting macrophages and migrate to infected macrophages and activated macrophages, infected macrophages tended to increase at the beginning of infection, activated macrophages is fluctuate, both young mice and old mice.

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**Table I.** Variables and initial values [3,7]

| Symbol | Description | Young | Old | Unit |
|---|---|---|---|---|
| $M_R$ | Density of resting macrophages | $5.10^5$ | $5.10^5$ | Cell/ml |
| $M_A$ | Density of activated macrophages | 200 | 1800 | Cell/ml |
| $M_I$ | density of infected macrophages | 1800 | 200 | cell/ml |
| $I_2$ | concentration of Interleukin-2 | 10 | 5 | pg/ml |
| $I_4$ | concentration of Interleukin-4 | 5 | 5 | pg/ml |
| $I_{12}$ | concentration of Interleukin-12 | 50 | 200 | pg/ml |
| $I_{10}$ | concentration of Interleukin-10 | 100 | 50 | pg/ml |
| TNF $\alpha$ | concentration of TNF $\alpha$ | 5 | 5 | pg/ml |
| IFN- $\gamma$ | concentration of IFN-$\gamma$ | 5 | 5 | pg/ml |
| $T_4$ | density of CD4+ T cells | $2.10^5$ | $10^5$ | cell/ml |
| $T_8$ | density of CD8+ T cells | $8.10^4$ | $8.10^4$ | cell/ml |
| $B_E$ | density of extracellular bacteria | 1000 | 1000 | cell/ml |
| $B_I$ | density of intracellular bacteria | 36000 | 4000 | cell/ml |

**Table 2.** Different parameters between young and old [7]

| Symbol | Description | Young | Old |
|---|---|---|---|
| $\lambda_x$ | rate of Major Histocompatibility Complex (MHC) I activation | 0,005266 ml/pg/day | 0,0022854 ml/pg/ day |
| $K_3$ | activation rate of infected macrophages | 0,023415/ day | 0,02544/day |
| $K_4$ | deactivation rate of activated macrophages | 0,28876/ day | 0,61707/day |
| $K_6$ | rate of activation of resting macrophages | 0,077068/ day | 0,13539/ day |
| $K_7$ | IL-10 production rate by infected macrophages | 0,5061/ day | 0,55044/ day |
| $K_8$ | IL-12 production rate by activated macrophages | 0,28503/ day | 0,53162/ day |
| $K_9$ | IL-12 production rate by resting macrophages | $5.10^{-4}$ pg/cell/ day | 0.001 pg/ cell day |
| $K_{10}$ | IL-2 production rate by CD4+ T cells | $2.1873.10^{-4}$ pg/cell/ day | $1.7301.10^{-4}$ pg/ cell day |
| $K_{11}$ | loss of IL-2 due to proliferation of CD4+ T cells | $1.6383.10^{-4}$ pg/sel/ day | $1.4788.10^{-4}$ pg/ cell day |
| $K_{12}$ | loss of IL-2 due to proliferation of CD8+ T cells | $1.6383.10^{-5}$ pg/cell/ day | $1.413.10^{-5}$ pg/ cell day |
| $K_{13}$ | rate of proliferation of CD4+ T cells by IL-2 | 0.1638 pg/cell/ day | 0.14789 pg/ cell day |
| $K_{14}$ | rate of proliferation of CD8+ T cells by IL-2 | 0.01638 pg/cell/ day | 0.01413 pg/ cell day |

**Table 3.** Parameter values [3,7]

| Symbol | Description | Range (Value) |
|---|---|---|
| $\alpha_8$ | IL-12 production by MA | $8x10^{-5}$ pg/ MA/day |
| $\alpha_{30}$ | TNF- $\alpha$ production by MI | $10^{-3} – 2x10^{-2}$ ($3x10^{-3}$) pg/ml MI day |
| $\alpha_{5c}$ | IFN-γ production by MI | 0.0002-0.0006 (0.0003) pg/ml MI |
| $\alpha_{4A}$ | TNF-independent recruitment of MR | $5x10^{-2}$/ day |
| $\alpha_{23}$ | IL-12 production by MR | $2.75x10^{-5} – 2.75x10^{-4}$ ($2x10^{-4}$) pg/ml MR |
| $\alpha_{31}$ | TNF- $\alpha$ production by MA | $0.3x10^{-4} – 1.5x10^{-4}$ ($4x10^{-3}$) pg/ml MA day |
| $\alpha_{32}$ | TNF- $\alpha$ production by CD4+ T cells | $8.16x10^{-4}$ pg/ml CD4/ day |
| $\alpha_{33}$ | TNF- $\alpha$ production by CD8+ T cells | $0.6x10^{-4}$ - $1.1x10^{-4}$ ($0.5x10^{-4}$) pg/ml CD8/ day |
| $Sr_{3B2}$ | TNF-dependent recruitment of CD4+ T cells | $10^3$/ day |

| | | |
|---|---|---|
| $Sr_{4B}$ | TNF-dependent recruitment of MR | $2x10^4$ MR/ day |
| $f_9$ | Ratio adjustment, TNF-$\alpha$/IL10 | 1 - 100 (50) |
| $f_7$ | Effect of IL-10 on IFN-γ -induced CD4+ T cells | 1 |
| $f_8$ | Ratio Adjustment, IL-10/TNF-$\alpha$ on MR Recruitment | 1 – 100 (1) |
| $S_{4b}$ | Half-sat, TNF-$\alpha$ on MR recruitment | 138 – 556 (200) pg/ml/ day |
| $C_{23}$ | Half-sat, BT on IL-12 by MR | $10^3$ - $5x10^6$ ($5x10^3$) BT/ml |
| $w_2$ | Max, percentage contribution of MI-produced chemokines to MR recruitment | 0.15 |
| $\mu_{Ty}$ | IFN-γ induced apoptosis rate of CD4+ T cells | $10^{-5}$– $10^{-3}$ ($10^{-4}$) /MA day |
| $\mu_{BI}$ | BI turnover to BE due to MI death, other mechanisms | 0 - 0.005 (0.004)/ day |
| $\mu_{TNF}$ | decay rate of TNF-$\alpha$ | 1.112/ day |
| $k_{14a}$ | Fas-FasL-induced apoptosis of MI | 0.01 - 0.1 (0.1) / day |
| $k_{14b}$ | TNF induced apoptosis of MI | 0.1 - 0.8 (0.1) / day |
| $s_{10}$ | Half-sat, IFN-γ on TNF-$\alpha$ production by MA | 50 - 100 (80) pg/ml |
| $\delta_7$ | IL-10 production by MA | 0.001 - 0.01 (0.01) pg/ml MA |
| $\alpha_{20}$ | BE growth rate | 0 - 0.26 (0.05) / day |
| $\alpha_{19}$ | BI growth rate | 0.17 - 0.6 (0.4) / day |
| $\alpha_{16}$ | IL-10 production by CD4+ T cells | $10^{-4}$– $10^{-3}$($2x10^{-2}$) pg/CD4 day |
| $S_{rM}$ | MR recruitment rate | 600 - 1000 (1000) MR/ day |
| $f_6$ | Adjustment, IFN-γ on IL-10 | 0.025-0.053 (0.025) |
| $f_4$ | Adjustment, IL-10/IL-12 on IFN-γ | 0.76 - 3.2 (2) |
| $f_1$ | Adjustment, IL-4/IFN-γ | 3 - 410 (200) |
| $s_2$ | Half sat., IL-4 | 1 - 10 (5) pg/ml |
| $s_6$ | Half-sat, IL-10 self-inhibition in MA | 51 - 60 (60) pg/ml |
| $s_4$ | Half-sat, IL-12 on IFN-γ | 50 - 100 (50) pg/ml |
| $s_7$ | Half-sat, IL-12 on IFN-γ by NK cells | 5 – 100 (40) pg/ml |
| $s_1$ | Half-sat, IFN-γ on MR to MA | 50 – 110 (70) |
| $c_9$ | Half-sat, BE on MR infection | $10^6$- $10^7$ ($2x10^6$) BE |
| $c_8$ | Half-sat, BT on MR activation | $5x10^4$ – $5x10^5$ ($10^5$) $B_T$/ml |
| $c_4$ | Half-sat, T cells /MI ratio for MI lysis | 1 – 60 (40) T/MI |
| $c_{10}$ | Half-sat, bacteria on IFN by NK cells | $10^3$ – $10^4$ ($10^3$) BT/ml |
| $\mu_{MR}$ | death rate of MR | 0.0033/ day |
| $\mu_{MI}$ | death rate of MI | 0.0011/ day |
| $\mu_{MA}$ | death rate of MA | 0.07/ day |
| $\mu_{I\gamma}$ | decay rate of IFN-γ | 2.16 - 33.2 (2.16) / day |
| $\mu_{I4}$ | decay rate of IL-4 | 2.77/ day |
| $\mu_{I10}$ | decay rate of IL-10 | 3.7 - 7.23 (5) / day |
| $\mu_{I12}$ | decay rate of IL-12 | 1.188/ day |
| $k_2$ | MR infection rate | 0.2 - 0.4 (0.4) / day |
| $k_3$ | MR activation rate | 0.2 - 0.4 (0.1) / day |
| $k_{17}$ | Max. MI death due to BI | 0.02 - 0.8 (0.02) / day |
| $k_4$ | MA deactivation by IL-10 | 0.01 - 0.4 (0.08) / day |
| $s_g$ | IFN-γ production by Natural killer (NK) cells | 0 – 1000 (100) pg/ml day |
| N | carrying capacity of infected macrophages | 10 – 100 (20) BI/MI |
| $\beta$ | scaling factor of TNF for MR to MA | $10^2$–$10^5$ ($10^2$) BT/pg |
| $\beta_2$ | scaling factor of BT for TNF-$\alpha$ production by MA | $10^{-3}$-$10^{-4}$ ($10^{-3}$) |
| $\lambda_u$ | rate of IFN-γ production by CD4+ T cells | $1.24 \times 10^{-4}$ pg/cell day |
| $\lambda_y$ | rate of IFN-γ production by CD8+ T cells | $1.24 \times 10^{-5}$ pg/ cell day |
| $\lambda_x$ | rate of MHCI activation | 0.005266 pg/ cell day |

| | | |
|---|---|---|
| $\lambda_z$ | rate of MHCII activation | 0.010532 pg/ cell day |
| $\alpha_{112}$ | IL-4 production by CD4+ T cells | $10^{-4}$ –9.1x$10^{-3}$ ($10^{-4}$) pg/CD4+ day |
| $k_4$ | deactivation rate of activated macrophages | 0.28876 / day |
| $k_{3A}$ | activated $M_I$ by INF-$\gamma$ | 0.023415 / day |
| $k_{7av}$ | IL-10 production rate by infected macrophages | 0.50610 pg/ml cell |
| $k_{10}$ | IL-2 production rate by CD4+ T cells | 2.187 ×$10^{-4}$pg/ cell day |
| $k_{11}$ | loss of IL-2 due to proliferation of *CD4*+ T cells | 1.6383 ×$10^{-4}$ pg/ cell day |
| $c_3$ | IFN-$\gamma$ inhibition for deactivation of activated macrophages | 3 |
| $c_{100}$ | saturation for T cell proliferation by IL-2 | 50 pg/ml |
| $c_{7a}$ | saturation for IL-10 inhibition by IL-10 | 5000 pg/ml |
| $\mu_{T4}$ | death rate of CD4+ T cells | 0.33 / day |
| $\mu_{T8}$ | death rate of CD8+ T cells | 0.33 / day |
| $\mu_g$ | decay rate of IFN-$\gamma$ | 2.16 –33.2 (2.16) / day |
| $a_2$ | saturation for activation of infected macrophage | 50 pg/m |
| $c_{81}$ | saturation for IL-12 inhibition by IL-10 | 200 pg/ml |
| n2 | average number of *BI* in an activated macrophages | 5 |
| n3 | threshold at which a resting macrophage becomes infected | 10 |
| μI2 | decay rate of IL-2 | 1.188/ day |
| $\alpha_{18}$ | IL-10 production by CD8+ T cells | $10^{-4}$– $10^{-3}$(2x$10^{-2}$) pg/CD8 day |

BE, extracellular bacteria; BI, intracellular bacteria; BT, total bacteria; Half-sat, half-saturation;
MA, activated macrophages; MI, infected macrophages; MR, resting macrophages.